Remarks

Claims 1-7 and 20-45 are pending. Claim 6 has been amended. Claims 8-19 are canceled. Claims 22-46 are newly added. Claim 6 was amended to correct the spelling of "occurring." Support for new claim 22 can be found throughout the application, and specifically on page 42, lines 1-4. New claims 23, 26, 29, and 32 find support at least in original claims 1 and 6. New claims 26, 29, and 32 also find support at least on page 36, lines 15-19 and 27-33. New claims 24, 27, 30, and 33 find support at least on page 36, lines 15-19 and 27-33. New claims 25, 28, 31, and 34 find support at least on page 37, lines 6-7. New claims 35-45 find support at least in Figures 11A, 11B, 11C, 11D, 11E, 11F, 11G, 14A, 19A, 24A, and 30A, respectively, and on page 15, lines 15-25 (claims 35-41), page 16, lines 17-21 (claim 42), page 18, lines 9-15 (claim 43), from page 20, line 29, to page 21, line 4 (claim 44), and page 23, lines 23-9 (claim 45).

A replacement section for the section "BRIEF DESCRIPTION OF THE DRAWINGS" is provided with this response. The only changes are to the description of Figure 11, where reference to the wrong figure numeral is made.

Rejections Under 35 U.S.C. § 112, First Paragraph

1. Claims 1-7 and 20-21 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

Claims 1-7 were considered to lack adequate written description on the basis that the specification and claims allegedly do not adequately describe the genus comprising regulatable gene expression constructs comprising riboswitches that are activated by a trigger molecule and produce a signal upon activation and which constructs further comprise a control strand, an aptamer domain, and an expression platform domain comprising a regulated strand.

Applicants respectfully traverse, first on the grounds that multiple examples of the genus of riboswitches have been provided, and second on the grounds that the premise of this rejection is not consistent with the law of written description.

A. Regarding the first point, the specification is replete with examples of structural features and sequence relationships of riboswitches. Importantly, the specification provides description of the key structural features and sequence relationships necessary for the operation of riboswitches in general, and provides multiple specific examples of such. For example, the specification (page 104, lines 13-20) states:

> Riboswitches that have been discovered are responsible for sensing metabolites that are critical for fundamental biochemical processes including adenosylcobalamin (AdoCbl) (see Example 1), thiamine pyrophosphate (TPP) (see Example 2), flavin mononucleotide (FMN), S-adenosylmethionine (SAM) (see Example 7), lysine (see Example 5) , guanine (see Example 6), and adenine (see Example 8). Upon interaction with the appropriate small molecule ligand, riboswitch mRNAs undergo a structural reorganization that results in the modulation of genes that they encode.

In each of the examples mentioned above, a detailed description of the riboswitch activated by a trigger molecule is given, along with an explicit discussion of how a trigger molecule interacts with the riboswitch. Thus, Applicants have described the general structure and operation of riboswitches; have identified the component parts of riboswitches, how they interconnect and operate, and how they can be recombined to form other riboswitches; and have provided a number of examples of riboswitches spanning a variety of genes and trigger molecules, thus solidifying both the validity of the general description and providing a representative number of examples of the structure of riboswitches. The numerous examples and consensus sequences provided clearly demonstrate Applicants' possession of the broad general subject matter of the present claims. It is hard to imagine how an applicant could provide more descriptive information of a pioneering invention than Applicants have provided.

The Office Action alleges that the specification and claims do not adequately describe the concise structural features (e.g., polynucleotide sequences, structures of all component parts of the gene expression constructs) that distinguish structures within the broadly claimed genus from those without. The Office Action states that the specification teaches the 5'-UTR of the B. subtilis xpt-pbuX mRNA as a guanine-responsive riboswitch. The Office Action goes on to state that the specification also teaches a comparison between the 5'-UTR fragment (of 185 nucleotides) and other bacterial sequences, whereby a conserved RNA motif, termed a "G box"

has been identified as a domain for guanine riboswitches. The Office Action then alleges that conserved secondary and tertiary structures are likely a pre-requisite for adopting the required, yet undefined three-dimensional fold necessary for riboswitch function. The Office Action thus implies that a detailed secondary and tertiary structure must be described in the application. This is not the case.

First, Applicants note that riboswitches are made up of different domains that have different roles to play in the operation of the riboswitch. As fully described in the specification, riboswitches include an aptamer domain and an expression platform. The expression platform of riboswitches generally involves alternative stem structures. The principles of operation and application of platform domains are described in the specification. The formation of hybridized stem structures in RNA is well known in the art, and the examples and principles of the structure and operation of platform domains of riboswitches is described in the specification. The structure-function relationship of the stem structures of platform domains is thoroughly described in the specification and provides all that is required by the written description requirement for this element of the claims.

Aptamer domains are essentially RNA aptamers. RNA aptamers in other contexts have been known and described for many years. The aptamer domains of riboswitches bind to trigger molecules and communicate through the RNA strand to the platform domain. Applicants submit that aptamers can be used and applied in riboswitches based on the description provided in the specification. Applicants discovered that aptamers in riboswitches are modular and can be used and interchanged between riboswitches. As noted in the specification, the aptamer domain of the riboswitch readily adopts the required structure without interference from, and independent of, the other control structures of riboswitches, even in aptamer domains synthesized *in vitro*:

> These conclusions are drawn from the observation that aptamer domains synthesized in vitro bind the appropriate ligand in the absence of the expression platform (see Examples 2, 3 and 6). Moreover, structural probing investigations suggest that the aptamer domain of most riboswitches adopts a particular secondary- and tertiary-structure fold when examined independently, that is essentially identical to the aptamer structure when examined in the context of the entire 5′ leader RNA. This implies that, in many cases, the aptamer domain is a modular unit that folds independently of the expression platform (see Examples 2, 3 and 6).

Specification, page 30, lines 23-30.

Therefore, the generic primary and secondary structural features of riboswitches described in the specification produce the necessary three-dimensional structure, without the need for guidance or further description. This is borne out by Applicants' description and analysis of guanine-responsive riboswitches and their structure. Having identified an example of an aptamer in a guanine-responsive riboswitch (where the aptamer binds to guanine and related compounds), Applicants searched for, found, and identified consensus elements of other guanine aptamers in guanine-responsive riboswitches in other genes (see part C of Figure 41). The conservation and similarity of the primary sequence of aptamers in these riboswitches is strongly indicative that the higher level structure and aptamer function follow from the primary structure. Those of skill in the art would have been able to readily produce such functional riboswitches without concern for the three dimensional structure of the aptamer domain, because the three dimensional structure would have naturally folded into the correct orientation for functionality. Furthermore, as noted in the passage above, the aptamer domain can be a modular component that can be exchanged with other control sequences of the riboswitch. Because the aptamer domain can be exchanged with other control sequences, the riboswitch can comprise any aptamer. The specification comprises multiple examples of such aptamers (see, for example, Figures 11 and 41). Furthermore, aptamers in general are well known in the art and can be produced by known techniques, and are useful with the riboswitches disclosed in the specification.

B. Subsequent to Applicants' invention, it has been confirmed that the consensus primary and secondary structural elements described in the present application naturally produce the structure required for riboswitch function. Tertiary structures of five classes of riboswitches have been solved and published (guanine-, adenine-, TPP-, SAM-, and glucosamine-6-phosphate-responsive riboswitches). In each publication the authors note how well Applicants' models and probing data (which corresponds to the models and data described in the present application) fit with the tertiary structures. For example, Serganov et al., Chem. Biol. 11:1729-

1741 (2004), a copy of which is submitted with this Response, describes the crystal structure of add adenine-responsive riboswitch and the xpt guanine-responsive riboswitch. The add and xpt riboswitches are examples of riboswitches in the present application (see, for example, Figures 11E, 11F, 23, 24, 25 28, 35 and Examples 6 and 8). Serganov (2004) compares the crystal structure, and the functional significance of the structure revealed, with the conserved primary and secondary structural elements that characterize the adenine and guanine riboswitches. See, for example, Serganov et al. (2004) page 1737, second column, third and fourth paragraphs; page 1738, fist column, first, second and third paragraphs; and page 1738, second column, first paragraph. Serganov et al. (2004) confirms and concludes that the primary and secondary structural information and the conserved elements of adenine- and guanine-responsive riboswitches that were earlier identified have structural and functional significance in the crystal structure. For comparison to the crystal structure, a number of these passages in Serganov et al. (2004) refer to the primary and secondary structural information of citation number 24, Mandal & Breaker, Nature Struct. Mol. Biol. 11(1):29-35 (2004) (a copy of which is submitted with this Response) which describes some of that same structural information in the present application. For example, present Example 8 describes work reported in Mandal & Breaker and Figures 35-40 in the present application correspond to Figures 1-6, respectively, in Mandal & Breaker. Thus, Serganov et al. (2004) provides evidence that the conserved and consensus structural elements identified in the present application are significant in determining the crystal structure of the riboswitch.

Serganov et al., Nature 441:1167-1171 (2006), a copy of which is submitted with this Response, describes the crystal structure of the thiM thiamine pyrophosphate (TPP) responsive riboswitch. The thiM TPP-responsive riboswitch is one of the example riboswitches in the present application (see, for example, Figures 6B, 9A, 11B, 13A, and 13B and Example 2). Serganov (2006) compares the crystal structure, and the functional significance of the structure revealed, with the conserved primary and secondary structural elements that characterize the TPP riboswitches. See, for example, Serganov et al. (2006) page 1167, first column, last paragraph; page 1168, second column first paragraph; page 1168, second column, last paragraph; and page 1169, first column, third paragraph. Serganov et al. confirms and concludes that the primary and

secondary structural information and the conserved elements of TPP-responsive riboswitches that were earlier identified have structural and functional significance in the crystal structure. For comparison to the crystal structure, a number of these passages in Serganov et al. (2006) refer to the primary and secondary structural information of citation number 4, Winkler et al., Nature 419:952-956 (2002) (of record), which describes some of that same structural information in the present application. For example, present Example 2 describes work reported in Winkler et al. and Figures 6, 7, 8, 9A-C, and 13B in the present application correspond to Figures 1-5, respectively, in Winkler et al. Thus, Serganov et al. (2006) provides evidence that the conserved and consensus structural elements identified in the present application are significant in determining the crystal structure of the riboswitch.

A new class of riboswitch has also been identified based on the consensus primary and secondary structural elements describe in the present application, which confirms that riboswitch function predictably follows from the primary and secondary structural characteristics of the RNA. Kim et al., Proc. Natl. Acad. Sci. 104:16092-16097 (2007), a copy of which is submitted with this Response, describes the recently discovered 2'-deoxyguanosine-responsive riboswitch. The 2'-dG riboswitch was identified by searching sequences for primary and secondary structural elements based on the consensus structural elements of the guanine-responsive riboswitches that are described in the present application. In particular, Kim et al. refers to prior work with guanine- and adenine-responsive riboswitches as providing the basis of the identification of the new type of riboswitch, citing, for example, Mandal et al., Cell 113:577-586 (2003) (reference 26) (of record) and Mandal & Breaker, Nature Struct. Mol. Biol. 11(1):29-35 (2004) (reference 27). Example 6 in the present application describes work reported in Mandal et al. (2003) and Figures 23-29 in the present application correspond to Figures 1-7, respectively, in Mandal et al. (2003). As discussed above, present Example 8 describes work reported in Mandal & Breaker and Figures 35-40 in the present application correspond to Figures 1-6, respectively, in Mandal & Breaker. Once the 2'-dG riboswitch was identified in Kim et al. by these sequence and predicted secondary structural features, an example of a 2'-dG riboswitch was tested and determined to have the expected secondary structure and the expected riboswitch activity. Thus, Kim et al. also provides evidence that the consensus structural information provided in the

present application represents structural information that adequately distinguishes the claimed riboswitches from other, non-riboswitch molecules. Further, the consistency of Applicants' description and understanding of riboswitch structure and function in the present application to subsequent findings regarding, and examples of, riboswitches is clear evidence that Applicants' were in possession of the riboswitches as presently claimed.

Applicants have also continued to identify additional riboswitches based on the original description and features described in the present application. Examples of such continued work include Barrick and Breaker, Genome Biology 8:R239 (2007), and Weinberg et al., Nucleic Acids Research 35(14):4809-4819 (2007, copies of which are submitted with this Response. These publications show that the general description of a new class of regulatory element based in RNA provided in the present application identified and described all of the key features and functions of riboswitches such that riboswitches could be identified and distinguished from what came before. Blount & Breaker, Nature Biotechnology 24(12):1558-1564 (2006), and Tucker & Breaker, Current Opinion in Structural Biology 15:342-348 (2005), copies of which are submitted with this Response, are reviews that describe riboswitch structure and function. These publications show the consistency between the description provided in the present application and the continued in riboswitches since Applicants invention.

C. As mentioned above, the premise of the arguments in the Office Action is not consistent with the law of written description. Compliance with the written description requirement need not involve the specific disclosure of every permutation of an invention, but should be commensurate with knowledge that comprises the state of the art. For example, in Capon v. Eshhar v. Dudas, 76 USPQ2d 1078, 1082 (Fed. Cir. 2005), the court held that neither a complete nucleotide description nor operability of every permutation within a generally operable invention is required in order for an adequate written description of generically claimed nucleic acid constructs. Capon involved claims broadly drawn to nucleic acid constructs encoding a chimera of single-chain variable portions of antibodies and transmembrane lymphocyte signaling proteins. Both parties in an interference proceeding had appealed a decision by the Board of Patent Appeals and Interferences ("Board") that their specifications failed to provide an adequate

written description of the claimed constructs. In particular, the Board stated that it could not be known whether all the permutations and combinations covered by the claims would be effective for the intended purpose, and that the claims were too broad because they might include inoperative species. Specifically, the Board stated that the disclosure of specific examples provided in each party's specification, in the absence of any sequence information within the specification, did not provide adequate written descriptive support for the invention. In reversing the Board's decision, the court in Capon held that since specific examples of the production of specified chimeric genes were provided in the specification, it was not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim. The court also confirmed its long-standing precedent that the disclosure required to meet the written description requirement will vary with the nature and scope of the invention. In sum, the court in Capon concluded that knowledge in the art of the sequences of the nucleic acids that were joined to construct the chimeric DNA molecules, together with Appellants' disclosures of known methods for joining nucleic acid molecules to form chimeric DNAs, provided adequate written description of DNA molecules encoding chimeric receptors, and therefore recitation of exact nucleotide sequences was not required.

Applicants assert that this same logic applies to the claimed riboswitch constructs. Applicants have described the general structure and operation of riboswitches; have identified the component parts of riboswitches, how they interconnect and operate, how they can be recombined to form other riboswitches; and have provided a number of examples of riboswitches spanning a variety of genes and trigger molecules. Like the applicants' disclosures in Capon, Applicants have provided specific examples of riboswitches, as well as clear guidance of how to select the modular components thereof, such as the aptamer. Like the components of the chimeric DNAs in Capon, extensive sequence information is available for the claimed riboswitch components.[1]

[1] The fact that the relevant sequences in Capon were provided in the art rather in the specifications while Applicants here provide the riboswitch sequence information in the specification is not a relevant distinction. In fact, the inclusion of this sequence information in the present specification is more favorable for written description than was the case in Capon.

As with the Board's basis for alleged unpatentability in Capon, the present rejection is based on an allegation that some of the presented riboswitch sequences would not be functional. As stated by the court in Capon, it is not necessary that every permutation be effective in order for an inventor to obtain a generic claim, provided that the effect was sufficiently demonstrated to characterize the invention. This principle applies to the present invention and facts with equal force and effect. Applicants submit that riboswitches were well demonstrated in the specification, as evidenced by the lengthy discussion of riboswitches therein (see page 104, lines 13-20, and the examples referenced in this passage, for example). Applicants have provided a variety of example riboswitches (and riboswitch components) and have identified consensus sequences for a number of riboswitches, which clearly qualifies as concise structural features that define the riboswitches and their components.

The Examiner alleges that the examples given, and the generic description of riboswitches, comprising an aptamer domain and an expression platform, the generic descriptions of structure function relationships for some identified (and proposed) stem structures of platform domains, and the sequence comparisons between previously described riboswitches found in nature, and sequence databases, together do not provide the concise structural features required for the very broad genus of compounds claimed. Applicants first note again that, as in Capon, the recitation of exact nucleotide sequences is not required for every permutation and combination of the claimed constructs. Applicants also note that, as discussed extensively above, the present specification provides a significant amount of information, including both specific and generic sequences, for myriad riboswitches. It is not seen how this fails to provide the "concise structural features" required by the rejection. On the contrary, the rejection merely concludes without evidence or sufficient reasoning that the extensive structural information provided is inadequate.[2] It can only be concluded that the rejection is applying a per

[2] The rejection seems to dismiss the majority of Applicants' disclosure of multiple riboswitch sequences and consensus sequences on the apparent basis that the Examiner does not believe that the identified sequences will function as riboswitches. This allegation does not support the present rejection for a number of reasons. First, there is no basis for the Examiner's assertion and it thus has no weight for the question of written description. Second, Applicants have stated that such sequences represent functional riboswitches, and such statements are to be believed unless there is sufficient evidence or reasoning to doubt them. In fact, there are good reasons why Applicants identification of riboswitch sequences is credible and creditable. In particular, the conservation of these sequences

se requirement of a type rejected by the court in Capon for a certain quality of written description. Such a per se and unsupported requirement is not supported by either the statute or the caselaw. Applicants have provided a full and complete disclosure, commensurate with knowledge that comprises the state of the art. One of skill in the art would have been able to identify riboswitches, and the components thereof, needed to make the claimed constructs, based on the disclosure in the specification.

Furthermore, in Falkner v. Inglis, 79 USPQ2d 1001 (Fed. Cir. 2006), the Federal Circuit found that Applicant need not spell out every detail of an invention, but only enough to convince a person of skill in the art that the inventor possessed the invention. At issue in Falkner were claims to a poxvirus lacking essential genes, for use as a vaccine. Although the specification at issue in Falkner neither identified, nor provided the sequence of, any essential poxvirus gene, essential regions of poxvirus were known in the art. The court, upholding a Board decision, found that the claims were adequately described. In support of its decision, the court held that:

> (1) examples are not necessary to support the adequacy of a written description (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure.

Although the specification at issue in Falkner neither identified, nor provided the sequence of, any essential poxvirus gene, essential regions of poxvirus were known in the art. The court agreed that those of skill in the art could easily select essential poxvirus genes. This is significant for the present rejection. The rejection dismisses Applicants' argument that those of skill in the art could readily produce the claimed constructs based on Applicants disclosure. The rejection discounts this argument on the basis that "Applicant must be in possession at the time of filing of an adequate representation of species for the broad genus of compounds claimed, not merely have the ability to screen for such peptides." However, it is clear from Falkner that "possession" for written description purposes does not require actual possession (i.e., reduction to practice) nor even a structural description of all elements of an invention. The specification at

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at locations proximate to transcription units and coding regions strongly supports that these sequences have functional significance.

issue in Falkner did not describe any "essential genes" of any poxvirus, nor provide specific guidance for which genes of poxvirus were or were not essential. Nevertheless, the court in Falkner held that such specific description was not required to satisfy the written description requirement. Significantly, the court recognized that the fact that those of skill in the art could identify essential poxvirus genes (an identification found nowhere in the specification at issue in Falkner) was sufficient to satisfy the written description requirement. This is analogous to the present constructs where those of skill in the art could easily identify the claimed riboswitches by reference to Applicants' extensive disclosure. As a result, the present application satisfies the written description requirement for the present claims. For at least these reasons, the present rejections should be withdrawn.

2. Claims 1-7 and 20-21 were rejected under 35 U.S.C. § 112, first paragraph, because allegedly the specification, while being enabling for a method of searching for candidates of the genus comprising RNA comprising any riboswitch operably linked to a coding region, which riboswitch regulates expression of the RNA, and which riboswitch and coding region are heterologous to each other, and which riboswitch comprises an aptamer domain, a control strand and an expression platform domain comprising a regulated strand, and which regulated and/or control strands form a stem structure, and which riboswitch is optionally derived from a naturally occurring guanine-responsive riboswitch, and which riboswitch is activated by a trigger molecule and produces a signal upon activation by the trigger molecule, does not reasonably provide enablement for predictably making and designing the members of the broad genus of molecules claimed. Applicants respectfully traverse this rejection.

The Office Action maintains the argument that the "Applicant has not provided guidance in the specification toward a method of making and using a representative number of species of the expansive genus of molecules claimed." First of all, Applicants point out that the standard of "a representative number of species of the expansive genus of molecules claimed" differs from, and is insupportably stringent compared to, the true legal standard for enablement. The enablement requirement of 35 U.S.C. 112, first paragraph, is separate and distinct from the

description requirement. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116-17 (Fed. Cir. 1991), MPEP Section 2161.

The MPEP (Section 2164.02) states that, "For a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation. Proof of enablement will be required for other members of the claimed genus only where adequate reasons are advanced by the examiner to establish that a person skilled in the art could not use the genus as a whole without undue experimentation." In this case, the Examiner has not set forth sufficient reasons why the multiple and explicit examples given in the specification would not be applicable to the genus as a whole.

As previously stated, the specification (page 104, lines 13-20) states:

> Riboswitches that have been discovered are responsible for sensing metabolites that are critical for fundamental biochemical processes including adenosylcobalamin (AdoCbl) (see Example 1), thiamine pyrophosphate (TPP) (see Example 2), flavin mononucleotide (FMN), S-adenosylmethionine (SAM) (see Example 7), lysine (see Example 5) , guanine (see Example 6), and adenine (see Example 8). Upon interaction with the appropriate small molecule ligand, riboswitch mRNAs undergo a structural reorganization that results in the modulation of genes that they encode.

In each of the examples mentioned above, a detailed description of the riboswitch activated by a trigger molecule is given, along with an explicit discussion of how a trigger molecule interacts with the riboswitch. Thus, Applicants have described the general structure and operation of riboswitches; have identified the component parts of riboswitches, how they interconnect and operate, and how they can be recombined to form other riboswitches; and have provided a number of examples of riboswitches spanning a variety of genes and trigger molecules, thus solidifying both the validity of the general description and providing a representative number of examples of the structure of riboswitches. The numerous examples and consensus sequences provided clearly demonstrate Applicants have clearly provided representative examples of the genus of riboswitches and their components, together with a statement applicable to the genus as a whole, which is all the law requires.

The Office Action also alleges that, "the ability to test various sequences for their ability to cleave target nucleic acid strands in the presence of various ligands, and the postulation of required, yet undefined structural constraints for riboswitch activities is not representative of the ability to predictably make and use the broad genus of compounds claimed." The Office goes on to allege that the specification fails to provide any particular guidance which resolves the known unpredictability in the art associated with determining the necessary sequences and structural components for designing functional riboswitches. The Office Action does not acknowledge Applicant's previous statement that the generic primary and secondary structural features of riboswitches described in the specification produce the necessary three-dimensional structure, without the need for further guidance. Those of skill in the art would have been able to readily produce such functional riboswitches without concern for the three dimensional structure of such, because the three dimensional structure would have naturally folded into the correct orientation for functionality.

Applicants would like to point out that in order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support (MPEP 2164.04). The Examiner has not given any reason why the objective truth of statements given by Applicant are doubted.

The rejection fails to provide any evidence or convincing arguments why those of skill in the art would have difficulty following the guidance provided by the present specification. Rather, the rejection consists only of conclusory statements unsupported by evidence or logical rationale. In particular, the rejection makes the following unsupported conclusions: "it would require undue experimentation beyond that taught in the instant specification, to produce the

broad genus of compounds claimed, "Applicant has not provided guidance in the specification toward a method of making and using a representative number of species of the expansive genus of molecules claimed, "The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with determining the necessary sequence and structural components for designing functional riboswitches[3] encompassed by the very broad genus claimed, "the invention as claimed would require de novo determination of sequence and structural characteristics, by trial and error, based on the identification and characterization of a representative number of species of the genus of compounds claimed," and "The examples provided do not enable one to make and use the broad genus of compounds claimed without undue experimentation." These read as mere opinion of the examiner; not conclusions based on the law and facts. The only fact on which these conclusions rely is the alleged extreme breadth of the claims. However, broad claims do not per se lack enablement. In fact, if the embodiments of a broad claim can each be made without the need for undue experimentation, then the number of embodiments encompassed by the claims does not render the claims nonenabled. Thus, the basis of the present rejection does not lead to a proper conclusion that the present claims lack enablement.

The Office Action alleges that the quantity of experimentation required to practice the invention as claimed would require the de novo determination of sequence and structural characteristics, by trial and error, based on the identification and characterization of a representative number of species of the genus of compounds claimed, whereby riboswitches are identified, designed, and constructed. As previously stated, in assessing whether undue experimentation would be required to make and use the claimed constructs, it is important to focus on what would actually have to be done in order to make and use the constructs. The claimed constructs comprise a regulatable gene expression construct comprising a nucleic acid molecule encoding an RNA comprising a riboswitch operably linked to a coding region, wherein the riboswitch regulates expression of the RNA, wherein the riboswitch and coding region are

[3] Applicants note that there is no "known" unpredictability regarding riboswitch design, and the rejection presents no evidence that there is sufficient unpredictability to result in the need for undue experimentation, especially in view of the extensive description and guidance presented in the specification.

heterologous. Thus, one wishing to make and use the claimed constructs need only (1) obtain a riboswitch and a coding region and (2) operably link the two.

Applicants submit that practice of none of these steps would require undue experimentation and that the specification supports this conclusion. First, producing an RNA construct was well within the ability of those of skill in the art at the time of the invention and to do so would not have required undue experimentation. Applicant gives multiple examples in the specification of riboswitches that can be used with the claimed invention, and carefully outline the components thereof, and how they can be obtained and used (see, for example, page 35 line 23 through page 42 line 14 of the specification). Applicant gives detailed information regarding the domains of the riboswitch, including both the aptamer and the expression platform. Thus, producing a construct as claimed would not require undue experimentation. Second, using the constructs was within the ability of those of skill in the art at the time of the invention. Applicants submit that it would not have required undue experimentation for those of skill in the art to use such constructs, as constructs in general and their applications were not only well known in the art at the time of the invention, but clearly discussed in the specification.

For all of the above reasons, applicants submit that the present claims are fully enabled and that the present rejection does not provide persuasive evidence or argument to the contrary. Accordingly, the present rejection should be withdrawn.

Rejection Under 35 U.S.C. § 102

Claims 1-7 and 20 were rejected under 35 U.S.C. § 102(a) as being anticipated by Breaker et al. (Curr. Opin. Biotech 13:31-39, Feb. 1, 2002). Applicants respectfully traverse this rejection.

The claims are drawn to a regulatable gene expression construct comprising a nucleic acid molecule encoding an RNA comprising a riboswitch operably linked to a coding region, wherein the riboswitch regulates expression of the RNA, wherein the riboswitch and coding region are heterologous. Breaker et al. does not teach riboswitches at all, but instead teaches intramolecularly cleaving ribozymes. As disclosed in the specification, both an aptamer domain and an expression platform make up a riboswitch, as opposed to a ribozyme. Breaker et al.

teaches no such elements. Specifically, Breaker et al. does not disclose riboswitches operably linked to a coding region.

Furthermore, Breaker et al. do not teach or suggest that the disclosed constructs involve expression of RNA. The claims are specifically drawn to a riboswitch that regulates the expression of RNA, unlike the constructs of Breaker et al., which teach only constructs that have a catalytic function when bound by an effector. The various portions of Breaker et al. cited in the Office Action do not describe any riboswitch (or any genetic switch) that regulates expression of RNA as claimed. The text on pages 31 and 32 of Breaker et al. merely discuss catalytic RNAs, the possibility and usefulness of allosteric ribozymes if they can be produced, and the hope that allosteric ribozymes could be used in the future to make engineered constructs (the text on page 38 also discusses the hope that allosteric ribozymes could be used in the future to make engineered constructs). This is mere speculation is does not enable production or use of such constructs. The catalytic RNAs and allosteric ribozymes of Breaker et al. are not described in Breaker et al. as controlling RNA expression. Rather, Breaker et al. merely expresses the hope that such ribozymes could be used some day in genetic control systems. The text on page 38 of Breaker et al. specifically notes that this hoped for use "poses many challenges to ribozyme engineers." Figures 2 and 3 merely illustrate schemes for selecting and enriching active ribozymes. There is no control of RNA expression by the ribozymes in Figure 2 or 3. Accordingly, Breaker et al. fails to disclose at least two features of the claimed constructs: linkage of a riboswitch to a coding region and regulation of RNA expression by a riboswitch. Because Breaker et al. fails to disclose every limitation of the claimed constructs, Breaker et al. fails to anticipate the claims. Applicants therefore respectfully request withdrawal of this rejection.

Conclusion

Pursuant to the above amendments and remarks, reconsideration and allowance of the pending application is believed to be warranted. The Examiner is invited and encouraged to directly contact the undersigned if such contact may enhance the efficient prosecution of this application to issue.

It is believed that no fee is due with this submission. However, the Commissioner is hereby authorized to charge any fees which may be required to Deposit Account No. 14-0629.

Respectfully submitted,

NEEDLE & ROSENBERG, P.C.

_/Robert A. Hodges/_____
Robert A. Hodges
Registration No. 41,074

NEEDLE & ROSENBERG, P.C.
Customer Number 23859
(678) 420-9300
(678) 420-9301 (fax)

CERTIFICATE OF ELECTRONIC TRANSMISSION UNDER 37 C.F.R. § 1.8			
I hereby certify that this correspondence, including any items indicated as attached or included, is being transmitted via electronic transmission via EFS-Web on the date indicated below.			
Name of Person Mailing	Robert A. Hodges		
Signature	/Robert A. Hodges/	Date	January 14, 2008